Sodium–Glucose Cotransporter 2 Inhibitors and Risk of Bladder and Renal Cancer: Scandinavian Cohort Study

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There are concerns that sodium–glucose cotransporter 2 (SGLT2) inhibitors may increase risk of bladder cancer. Such an association was indicated early in the development of the drug class and was subsequently shown in meta-analyses of randomized trials (1) and in analyses of spontaneous reports (2), although the evidence is conflicting (3). Based on animal studies, concerns have also been raised regarding an increased risk of renal cancer. Randomized trials have shown an imbalance for this cancer among patients receiving SGLT2 inhibitors versus placebo or other glucose-lowering drugs (3).

We conducted a cohort study (April 2013–December 2018) using a new-user active comparator design and nationwide data in Sweden, Denmark, and Norway from the prescription drug registers, patient registers, cancer registers, population registers, national bureaus of statistics, the Swedish National Diabetes Register, and the Danish Register of Laboratory Results for Research. Data sources and general methods used have previously been described in detail (4,5).

The study was approved by the Regional Ethics Committee in Stockholm, Sweden, and the Regional Committee for Medical and Health Research Ethics, Oslo, Norway. In Denmark, ethics approval is not required for register-based research.

We included patients, aged 35–84 years, who filled their first prescription for either SGLT2 inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists (an active comparator that was chosen because it has no known associations with the investigated outcomes and was used in similar clinical situations [as second-line or third-line diabetes drugs], with both drug classes being recommended for patients at high cardiovascular risk during the study period)). Exclusion criteria were previously filled prescriptions for any study drug; history of urinary tract cancer (including bladder carcinoma in situ), cystectomy, dialysis or renal transplantation, end-stage illness, or severe pancreatic disorders; hospitalization within 30 days before cohort entry; no recorded specialist care contact or prescription drug in the year preceding cohort entry (to exclude those with potentially incomplete information regarding medical history and prescription drug use); and biopsy/resection of the kidney or bladder, drug misuse, or any incident cancer (except nonmelanoma skin cancer) in the year preceding cohort entry.

Using logistic regression, we estimated country-specific propensity scores based on 40 covariates at cohort entry, including sociodemographic characteristics, comorbidities, comedications, and health care use (data on file). Patients with nonoverlapping propensity scores were trimmed from the cohort.

We performed separate analyses for the two study outcomes, identified from the national cancer registers: bladder cancer (including in situ; ICD-10 codes C67 and D09.0) and renal cancer (C64 and C65). We used an intention-to-treat exposure definition, and patients were followed from cohort entry until outcome

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Table 1—Primary, additional, and sensitivity analyses of association between use of SGLT2 inhibitors versus GLP-1 receptor agonists and risk of bladder cancer and renal cancer

	SGLT2 inhibitors			GLP-1 receptor agonists					
	n	*n* events	*n* events per 10,000 person-years	*n*	*n* events	*n* events per 10,000 person-years	Crude HR (95% CI)	Adjusted* HR (95% CI)	Adjusted absolute rate difference, *n* events (95% CI) per 10,000 person-years
Bladder cancer									
Primary analysis (1 year lag)	57,383	73	8.2	49,398	70	6.9	1.19 (0.85–1.65)	0.88 (0.59–1.31)	−0.8 (−2.8 to 2.1)
Additional analyses by years since treatment initiation									
All years	89,799	139	8.6	65,200	108	6.8	1.25 (0.97–1.61)	0.98 (0.72–1.33)	−0.1 (−1.9 to 2.2)
<1 year	89,799	66	9.0	65,200	38	6.6	1.35 (0.90–2.01)	1.15 (0.72–1.84)	1.0 (−1.9 to 5.6)
1 to <3 years	57,383	60	8.5	49,398	53	7.3	1.18 (0.81–1.70)	0.81 (0.52–1.26)	−1.4 (−3.5 to 1.9)
≥3 to 5 years	18,669	13	7.0	24,459	17	5.8	1.22 (0.59–2.53)	1.32 (0.60–2.90)	1.8 (−2.3 to 11.0)
Sensitivity analyses†									
Truncation of weights >10	57,383	73	8.2	49,398	70	6.9	1.19 (0.85–1.65)	0.88 (0.59–1.31)	−0.8 (−2.8 to 2.1)
Trimming of lowest and highest 2.5 percentiles of propensity score	54,885	68	8.0	46,753	69	7.2	1.10 (0.79–1.54)	0.90 (0.62–1.32)	−0.7 (−2.7 to 2.3)
Exclusion of patients with any previous cancer	54,307	68	8.0	46,731	64	6.6	1.20 (0.85–1.69)	0.92 (0.61–1.39)	−0.5 (−2.6 to 2.6)
Censoring users of GLP-1 receptor agonists at initiation of SGLT2 inhibitors	57,383	73	8.2	44,917	59	7.3	1.13 (0.80–1.59)	0.82 (0.54–1.26)	−1.3 (−3.4 to 1.9)
Exclusion of patients with previous pioglitazone use	55,771	67	8.0	47,986	69	6.8	1.17 (0.83–1.64)	0.85 (0.56–1.28)	−1.0 (−3.0 to 1.9)
Propensity score with additional variables (Sweden)‡	37,881	32	10.7	35,710	38	7.5	1.46 (0.91–2.35)	1.24 (0.72–2.13)	1.8 (−2.1 to 8.5)
Propensity score with additional variables (Denmark)§	24,770	11	4.6	17,275	15	5.1	0.83 (0.38–1.83)	0.78 (0.32–1.88)	−1.1 (−3.5 to 4.5)
Renal cancer									
Primary analysis (1 year lag)	57,393	64	7.2	49,404	58	5.7	1.30 (0.91–1.85)	1.09 (0.73–1.63)	0.5 (−1.5 to 3.6)
Additional analyses by years since treatment initiation									
All years	89,799	114	7.0	65,200	87	5.5	1.32 (0.99–1.75)	1.13 (0.82–1.56)	0.7 (−1.0 to 3.1)
<1 year	89,799	50	6.8	65,200	29	5.1	1.35 (0.86–2.14)	1.20 (0.70–2.05)	1.0 (−1.5 to 5.3)
1 to <3 years	57,393	52	7.4	49,404	39	5.4	1.41 (0.93–2.14)	1.10 (0.69–1.76)	0.6 (−1.7 to 4.1)
≥3 to 5 years	18,678	12	6.5	24,478	19	6.5	1.00 (0.49–2.07)	1.04 (0.47–2.30)	0.3 (−3.4 to 8.4)
Sensitivity analyses†									
Truncation of weights >10	57,393	64	7.2	49,404	58	5.7	1.30 (0.91–1.85)	1.09 (0.73–1.63)	0.5 (−1.5 to 3.6)
Trimming of lowest and highest 2.5 percentiles of propensity score	54,893	62	7.2	46,760	54	5.6	1.33 (0.92–1.92)	1.08 (0.72–1.63)	0.4 (−1.6 to 3.5)
Exclusion of patients with any previous cancer	54,318	61	7.2	46,732	53	5.5	1.35 (0.93–1.95)	1.14 (0.75–1.72)	0.8 (−1.4 to 4.0)
Censoring users of GLP-1 receptor agonists at initiation of SGLT2 inhibitors	57,393	64	7.2	44,925	48	5.9	1.23 (0.84–1.79)	0.97 (0.64–1.48)	−0.2 (−2.1 to 2.8)

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Table 1—Continued

	SGLT2 inhibitors			GLP-1 receptor agonists					
	n	*n* events	*n* events per 10,000 person-years	*n*	*n* events	*n* events per 10,000 person-years	Crude HR (95% CI)	Adjusted* HR (95% CI)	Adjusted absolute rate difference, *n* events (95% CI) per 10,000 person-years
Propensity score with additional variables (Sweden)‡	37,881	16	5.4	35,710	21	4.2	1.33 (0.69–2.55)	1.10 (0.50–2.39)	0.4 (−2.1 to 5.8)
Propensity score with additional variables (Denmark)§	24,770	17	7.1	17,275	19	6.4	1.26 (0.65–2.45)	1.15 (0.56–2.35)	1.0 (−2.8 to 8.6)

*Adjusted using propensity score standardized mortality ratio weighting. †The sensitivity analyses in which weights were truncated or trimmed were performed because extreme propensity score weights can be assigned to users of GLP-1 receptor agonists with low propensity scores. The sensitivity analysis excluding all patients with history of any cancer (except nonmelanoma skin cancer) were performed because such patients might be subject to more clinical investigations, which may affect time to tumor detection. The sensitivity analysis in which users of GLP-1 receptor agonists were censored at switch to or add-on therapy with SGLT2 inhibitors was performed to avoid exposure misclassification. All sensitivity analyses were performed with the same methodology as used in the primary analysis. ‡Weighted analyses where a propensity score was used including additional variables with data from the Swedish National Diabetes Register (glycated hemoglobin, estimated glomerular filtration rate, albuminuria, BMI, blood pressure, and smoking) in Sweden. The Sweden adjusted HR without use of these additional variables was 1.18 (95% CI 0.70–1.97) for bladder cancer and 1.15 (0.55–2.44) for renal cancer. §Weighted analyses where a propensity score was used including additional variables with data from the Danish Register of Laboratory Results for Research (glycated hemoglobin, estimated glomerular filtration rate, and albuminuria) in Denmark. The Denmark adjusted HR without use of these additional variables was 0.75 (0.30–1.85) for bladder cancer and 1.17 (0.58–2.38) for renal cancer.

event, death, emigration, 5 years of follow-up, or end of study period. Using standardized mortality ratio propensity score weighting and Cox proportional hazards regression with sandwich estimator for SEs, we estimated hazard ratios (HRs) for use of SGLT2 inhibitors versus GLP-1 receptor agonists. For accounting for cancer latency and reduce risk of reverse causation, HRs were estimated from 1 year after treatment initiation.

The cohort included 89,799 new users of SGLT2 inhibitors (proportion of follow-up time by drug: dapagliflozin 59%, empagliflozin 40%, canagliflozin 0.8%, ertugliflozin <0.1%) and 65,200 new users of GLP-1 receptor agonists. After propensity score weighting, treatment groups were well-balanced on baseline characteristics (mean age 62 years, 64% men, 21–22% using insulin [data on file]). In the analyses of bladder cancer, 57,383 users of SGLT2 inhibitors and 49,398 users of GLP-1 receptor agonists remained at risk at 1 year after treatment initiation. The corresponding numbers in the analyses of renal cancer were 57,393 and 49,404. Median follow-up time was 2.3 years (interquartile range 1.6, 3.4) for SGLT2 inhibitors and 3.0 years (1.9, 4.2) for GLP-1 receptor agonists.

Use of SGLT2 inhibitors, as compared with GLP-1 receptor agonists, was not associated with a statistically significant increase in risk of bladder cancer (adjusted HR 0.88 [95% CI 0.59–1.31]) or renal cancer (adjusted HR 1.09 [95% CI 0.73–1.63]) (Table 1). In additional analyses, the adjusted HR did not increase with time since cohort entry (Table 1). In several sensitivity analyses, including those with adjustment for additional variables such as smoking and glycated hemoglobin, the findings did not differ materially from those of the main analyses (Table 1).

In this cohort study including almost 150,000 patients from nationwide registers in three countries, use of SGLT2 inhibitors was not associated with an increased risk of bladder cancer or renal cancer. The upper limits of the CIs were inconsistent with a relative risk increase of >31% for bladder cancer and 63% for renal cancer.

The safety signals arose from analyses where cancer latency was not accounted for and clinical trial data used were from selected populations whose small size and short follow-up

time limit the possibility of assessing cancer events (1,3). In our analyses of events occurring at least 1 year after treatment initiation, 73 bladder cancer events and 64 renal cancer events occurred among SGLT2 inhibitor users during a median follow-up of 2.3 years, with >20% of these patients having >3 years of follow-up. In additional analyses, there was no indication of an increased risk after ≥3 to 5 years since treatment initiation. Conversely, while it has also been suggested that SGLT2 inhibitors may increase the short-term risk of the investigated outcomes due to effects on preexisting cancers or the probability of an early diagnosis, we did not observe a significantly increased risk in analyses restricted to the first year after treatment initiation.

Limitations of the study include the risk of unmeasured and residual confounding and potential outcome misclassification, although the Scandinavian cancer registers have high completeness and accuracy. Moreover, although there was no indication of an increased risk after ≥3 years since treatment initiation in our additional analyses, future studies with longer follow-up and assessment of individual SGLT2 inhibitors separately should be performed. In the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial, a protective association between randomization to dapagliflozin, versus placebo, and bladder cancer was observed, and SGLT2 inhibitors have reduced tumor growth in vivo and in vitro in certain cancers, including renal cell carcinoma.

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Data and Resource Availability. Study definitions and descriptive statistics are available on request.

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